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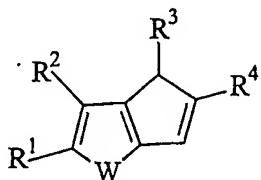
WO 03/014107 A1

(54) Title: PROCESS FOR THE PREPARATION OF HETEROCYCLIC PENTALENE DERIVATIVES

(57) Abstract: A process for preparing heterocyclic pentalene derivative having formula (I): wherein w is a sulfur atom (S), an oxygen atom (O) or a NR or PR group, wherein R is an hydrocarbon group; R¹, R², R³, and R⁴, equal to or different from each other, are hydrogen atoms or hydrocarbon groups; said process comprising the following steps: a) contacting a compound of formula (II) T is a OR, NR₂, CCl₃, CF₃, C1, Br, I, imidazolil or pirazolyl radical; with at least one molar equivalent of a vinyl compound of formula (III): wherein M is MgHal, Li, K, ZnHal, wherein Hal is chlorine, bromine or iodine; (II), (III) b) treating the compound of formula obtained in step a) with a Bronsted acid; c) treating the compound obtained in step b) with a reducing agent; and d) dehydrating the alcohol obtained in step c) in order to obtain the compound of formula (I).

PROCESS FOR THE PREPARATION OF HETEROCYCLIC PENTALENE DERIVATIVES

The present invention relates to a new process for preparing heterocyclic pentalenes derivatives of formula:



wherein R¹, R², R³ and R⁴ represent hydrogen or hydrocarbon rests and W is an oxygen atom, a sulfur atom or a NR or PR group and R is an hydrocarbon rest.

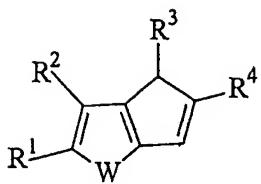
Heterocyclic pentalenes are well known in the art for various uses. For example substituted thiophenes and b, d-ortho-fused thiophenes are used as reference materials in the analysis of sulphur-containing substances of fossil raw materials, such as mineral oils, coal, carbonaceous oils, shale oils and tar sands, as model systems for studying the desulphurisation of the aforementioned fossil raw materials, also on a technical scale, as oxidation inhibitors, for example in lubricants and as active substances in the fields involving biocides.

Recently they have been used for the preparation of metallocene complexes useful as catalysts for the polymerization of olefins. For example in J. Am. Chem. Soc. 1998, 120, 10786-10787 Ewen et al. describe metallocene compounds containing thiopentalene and azapentalene derivatives. Also PCT/EP00/12406 describes metallocene compounds containing thiopentalenes ligands. Catalyst based on these compounds produce polypropylene having a high degree of isotacticity. However the synthesis of these compounds involves several steps with low yields and, moreover, some derivatives are not accessible according to the routes proposed in these documents.

Therefore, a new process that permits to obtain these compounds in higher yields and with simple steps would be desirable.

The applicant has now found a new process that permits to overcome the above drawbacks and, moreover, to obtain a broader class of compounds.

An object of the present invention is a process for preparing heterocyclic pentalene derivatives having formula (I):



(I)

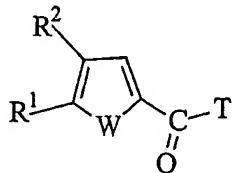
wherein

W is a sulfur atom, an oxygen atom or a NR or PR group wherein R is a linear or branched saturated or unsaturated C₁-C₂₀-alkyl, C₃-C₂₀-cycloalkyl, C₆-C₂₀-aryl, C₇-C₂₀-alkylaryl or C₇-C₂₀-arylalkyl radical, optionally containing heteroatoms belonging to groups 13-17 of the Periodic Table of the Elements; preferably the group NR is N-methyl or N-phenyl; and the group PR is P-methyl or P-phenyl; more preferably W is a sulfur atom;

R¹, R², R³ and R⁴, equal to or different from each other, are hydrogen atoms or a linear or branched saturated or unsaturated C₁-C₂₀-alkyl, C₃-C₂₀-cycloalkyl, C₆-C₂₀-aryl, C₇-C₂₀-alkylaryl or C₇-C₂₀-arylalkyl radical, optionally containing heteroatoms belonging to groups 13-17 of the Periodic Table of the Elements; or R¹ and R² and/or R³ and R⁴ can form a C₄-C₇ ring optionally containing O, S, N, P or Si atoms, said ring optionally bearing C₁-C₂₀ alkyl substituents or being optionally fused with a C₄-C₇ ring optionally containing O, S, N, P or Si atoms, such as a benzene or a cyclopentadiene ring; preferably R¹ is hydrogen, a C₁-C₂₀-alkyl or C₇-C₂₀-arylalkyl radical; more preferably R¹ is a methyl, a phenyl or a C₁-C₁₀ alkyl substituted phenyl radical; preferably R² is hydrogen or a C₇-C₂₀-arylalkyl radical; more preferably R² is a phenyl or a C₁-C₁₀ alkyl-substituted phenyl radical; preferably R³ is hydrogen or a C₁-C₂₀-alkyl radical; and preferably R⁴ is hydrogen, a C₁-C₂₀-alkyl or C₇-C₂₀-arylalkyl radical; more preferably R⁴ is a methyl, or a phenyl radical;

said process comprising the following steps:

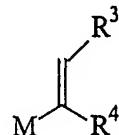
a) contacting a compound of formula (II):



(II)

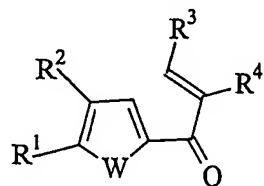
wherein R¹ and R² are defined as above and T is a OR, NR₂, OH, CCl₃, CF₃, Cl, Br, I, imidazolyl or pirazolyl radical;

with at least one molar equivalent of a vinyl compound of formula (III):



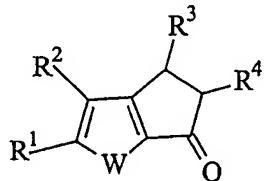
(III)

wherein R³ and R⁴ are defined as above and M is MgHal, Li, K, ZnHal, wherein Hal is chlorine, bromine or iodine; to form a compound of formula (IV):



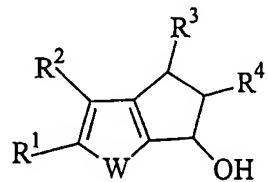
(IV)

b) treating the compound of formula (IV) with a Brønsted acid to form a compound of formula (V):



(V)

c) treating the compound of formula (V) with a reducing agent to form the correspondent alcohol of formula (VI);

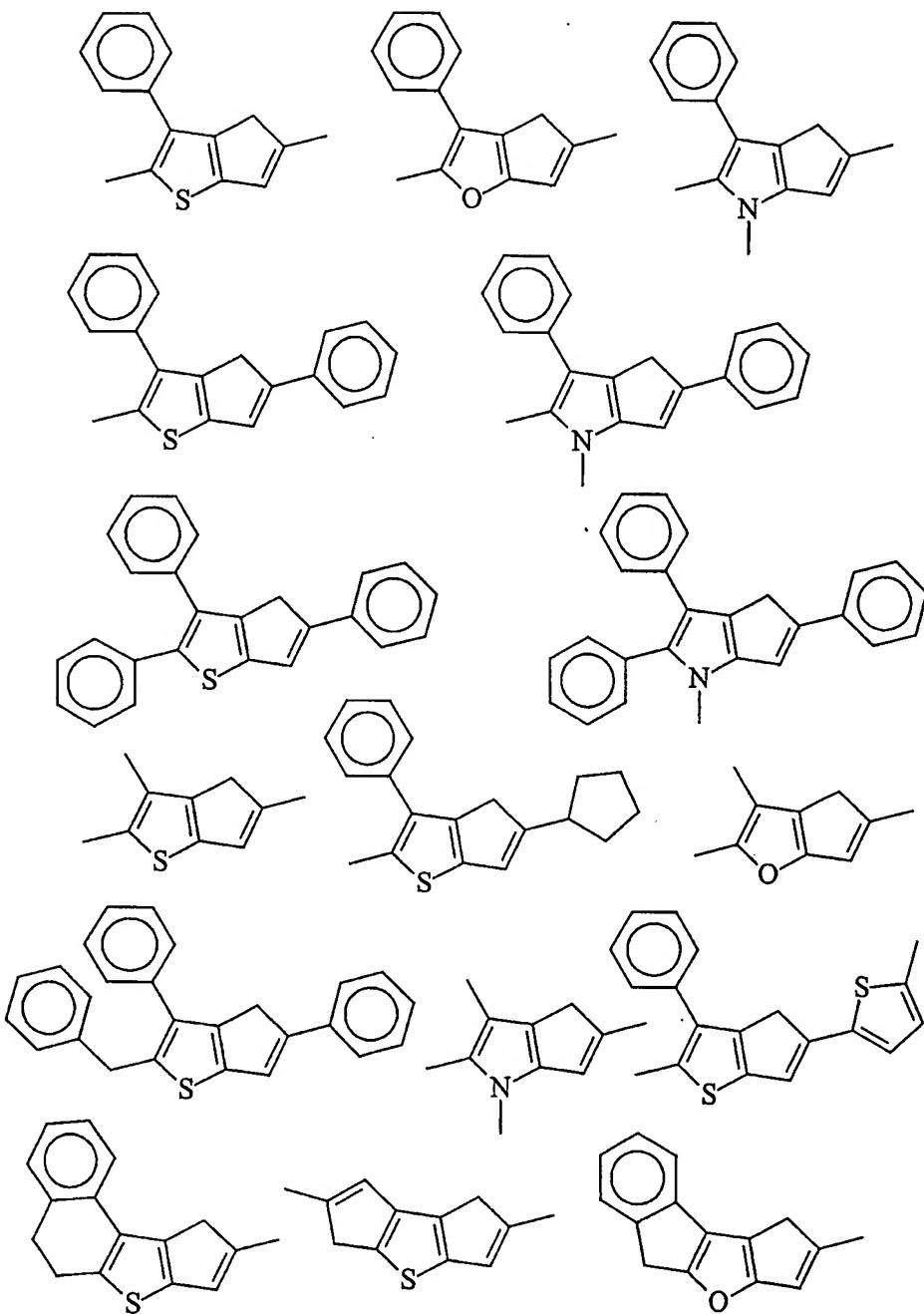


(VI)

and

d) dehydrating the alcohol of formula (VI).

Non limitative examples of compounds of formula (I) are:



Compounds of formula (II) used in step a) can be prepared with methods generally known in the art. For example when W is a sulfur atom these compounds can be prepared according to the process described in J. Chem. Soc. Perkin 1, 1976, vol. 22, 2355-2360.

Compounds of formula (III) can be easily prepared starting from the correspondent vinyl bromide or they can be purchased as such.

Step a) is carried out at a temperature range of from -78 °C to 100°C, preferably from -20°C to

20°C. Usually aprotic solvents are used, such as toluene, diethyl ether, hexane, tetrahydrofuran, dimethyl formamide, etc. The product obtained from step a) is purified by process known in the art such as filtration, crystallization, chromatography, distillation; otherwise it is used as such.

Preferably in the compound of formula (II) T is a NR₂ group; more preferably T is a N(Me)₂ or a N(Et)₂ radical. In the compound of formula (III) preferably the group M is MgBr or Li. Examples of Brønsted acid used in step b) are methanesulphonic acid, sulfuric acid, phosphoric acid, polyphosphoric acid or P₂O₅/methansulfuric acid. Preferably methanesulphonic acid or sulfuric acid are used. The reaction is preferably carried out in water or in an organic solvent such as dichloromethane, diethyl ether, tetrahydrofuran, dimethyl formamide, or in mixtures of water and organic solvents optionally in the present of a phase transfer agent. The reaction is carried out at a temperature range from 0°C to 100°C. The amount of acid in step b) depends from the acid, usually a large excess of acid is used for example from 10 to 10000 equivalents or more.

The product obtained from step b) is purified by processes known in the art such as filtration, crystallization, chromatography, distillation; otherwise it is used as such.

Examples of reducing agents that can be used in step c) can be found in "Comprehensive Organic Transformations" ed. 1989 VCH Publishers pages 527-552. For example LiAlH₄, AlH₃, NaBH₄ or LiHAL(OtBu)₃ can be used. Preferably LiAlH₄ is used.

The type of solvent used in step c) depends from the reducing agent used. In the case of LiAlH₄, AlH₃, NaBH₄ or LiHAL(OtBu)₃ the reaction is carried out in an aprotic solvent such as toluene, diethyl ether, hexane, tetrahydrofuran, dimethyl formamide, at a temperature range of from -78°C to 100°C, preferably from 0°C to 80°C. The product obtained from step c) is purified by processes known in the art such as filtration, crystallization, chromatography, distillation; otherwise it is used as such.

Step d) is carried out by treating the alcohol of formula (VI) with a dehydrating agent. Examples of dehydrating agent can be found in "Comprehensive Organic Transformations" ed. 1989 VCH Publishers pages 151-153. Example of dehydrating agent are p-toluenesulfonic acid, sulfuric acid, hydrochloric acid and iodine. Preferably p-toulensulfonic acid and iodine are used.

The amount of dehydrating agent depends from the dehydrating agent used. It can vary from one equivalent to a large excess such as 1000 equivalents and more.

The type of solvent used in step d) depends from the dehydrating agent used. In the case of p-toulensulfonic acid the reaction is carried out in an aprotic solvent such as toluene, diethyl ether, hexane, tetrahydrofuran, dimethyl formamide, at a temperature range of from 0°C to 100°C, preferably from 20°C to 80°C. The product obtained from step d) is purified by processes known in the art such as filtration, crystallization, chromatography, distillation. A further method for purifying compounds obtained in step d) is treating the crude reaction product with at least one equivalent of an organolithium compound such as butyllithium, methyllithium, tertbutylolithium and phenyllithium and filtering the obtained salt.

Steps a), b, c) and d) of the process of the present invention may be carried out in sequence without purification of the intermediate products.

Preferably steps c) and d) are carried out "one pot", i.e. without purification of the alcohol of formula (VI).

Compounds of formula (I) can be used as ligands for the synthesis of metallocene complexes, such as those described in WO 01/44318. These complexes are useful as catalyst components for polymerizing alpha-olefins. The syntheses of the metallocene compounds starting from the compounds of the present invention are described in the above mentioned application. Generally, the compounds of formula (I) can be treated with a base and then contacted with a compound of formula $YL'Cp$ wherein Y is halogen, preferably chlorine, L' is a suitable bridge and Cp is a substituted or unsubstituted cyclopentadienyl radical. The obtained bridged ligand is then treated with two equivalents of a base and contacted with the compound of formula ML''_4 wherein M is titanium, zirconium or hafnium and L is generally halogen, preferably chlorine. For unbridged metallocene compounds the compound of formula (I) is treated with a base and then the correspondent anion is contacted with a compound of formula ML''_4 .

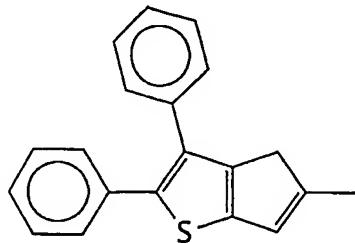
The following examples are given for illustrative purposes and are not intended to limit the scope and spirit of the invention.

EXAMPLES

General procedures.

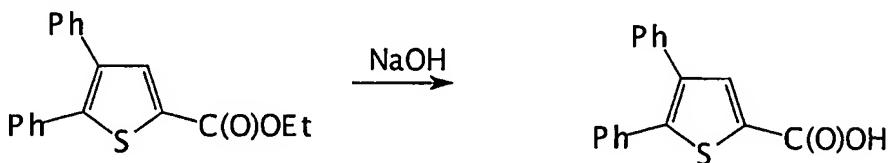
Operations moisture sensitive were performed under nitrogen by using conventional Schlenk-line techniques. Solvents were purified by degassing with N_2 and passing over activated (8 hours, N_2 purge, 300 °C) Al_2O_3 , and stored under nitrogen. *n*-BuLi (Aldrich) was used as received.

Example 1 Synthesis of 2,3-diphenyl-5-methyl-6H-cyclopenta[b]thiophene



Preparation of the compound of formula (II)

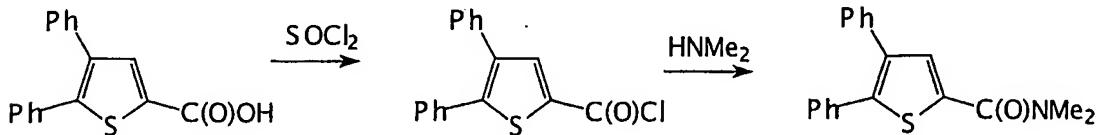
Synthesis of 2,3-Diphenyl-thienylcarbonyc acid



30.8g (0.1mol) of 2,3-diphenyl-5-carbetoxythiophene (prepared analogously to 2-methyl-3-phenyl-5-carbetoxythiophene with 70-80% yield from deoxybenzoin) was treated with solution of 20g NaOH in 50ml water+50ml ethanol. Resulting mixture was refluxed in 3h and then was treated with 100 ml water. Aqueous phase was collected, added with HCl aq. up to pH=3. White solid was isolated by filtration, washed with 100ml water and dried. Yield 100%.

¹H NMR (Dimethylsulfoxide (DMSO)-d₆): 7.76 (s, 1H), 7.40-7.20 (m, 10H), 3.5 (br.s., water + acidic proton)

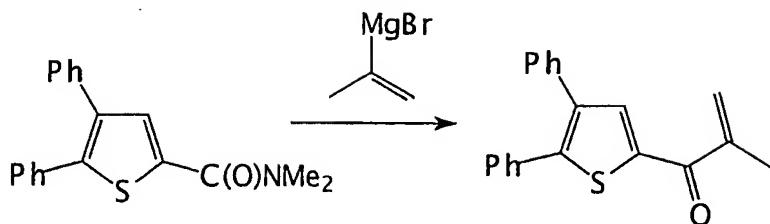
Synthesis of 2,3-Diphenyl-thienylcarbonyc acid dimethylamide



10g (36mmol) of acid, 5.5ml SOCl₂ (75mmol), 0.1ml dimethylformamide (DMF) and 50 ml of benzene were placed into the bulb and refluxed in 2h. Then the mixture was evaporated. Resulting oil was dissolved in 10ml of tetrahydrofuran (THF) and this solution was added dropwise to 30ml 33% aqueous Me₂NH at 0°C. The mixture was stirred in 30min. The precipitate was isolated, washed with water and dried. Yield 10g (92%).

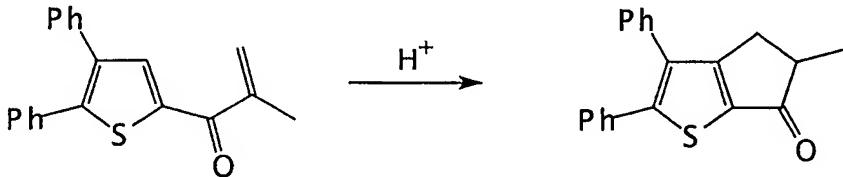
¹H NMR (CDCl₃): 7.45 (s, 1H), 7.40-7.20 (m, 10H), 3.40-3.20 (br.s., 6H)

Step a) 1-(4,5-Diphenyl-2-thienyl)-2-methyl-2-propen-1-on



10g (33mmol) of 2,3-Diphenyl-thienylcarbamic acid dimethylamide was dissolved in 15ml THF and the resulting solution was added dropwise to solution of propenylmagnesium bromide prepared from 0.78 g Mg (33mmol) and 4g 2-bromopropene (33mmol) in 50ml THF at -40°C. The mixture warmed to r.t. and was stirred in 4h. The resulting solution was poured into 100ml of 5% aqueous HCl. The organic layer was collected, washed with water, dried over MgSO₄ and evaporated to give yellow-reddish oil. Yield 9.5g (100%). The product is contaminated with 5-10% of starting amide (by NMR) and can be used without further purification.

Step b) 5-Methyl-2,3-diphenyl-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on

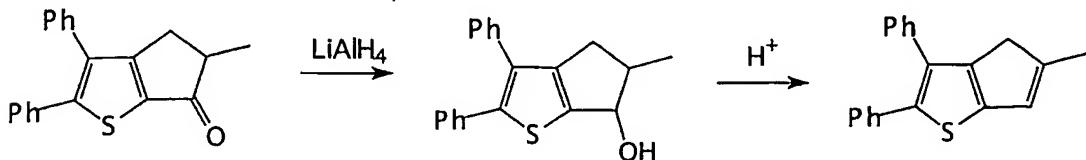


Solution from previous experiment was poured into 80 ml methanesulphonic acid (can be replaced by H₂SO₄) at 65°C. After 30 min of stirring at reflux the resulting mixture was poured into 400ml water/300ml dichloromethane mixture. The organic phase was collected, washed with aq. NaHCO₃ up to neutral reaction and dried over MgSO₄. The resulting solution was evaporated to give 8.8g viscous oil. This substance either have to be purified by chromatography on silica gel with benzene as an eluent (*R*_f of the product is ~ 0.15) or can be used as is.

¹H NMR (CDCl₃): 7.40-7.20 (m, 10H), 3.20 (dd, 1H), 3.06 (quintet of doublets, 1H), 2.67 (dd, 1H), 1.44 (d, 3H)

Steps c) and d)

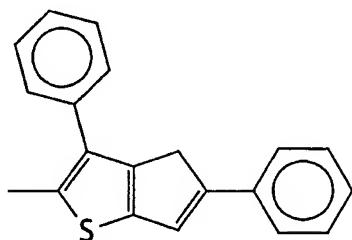
5-Methyl-2,3-diphenyl-4H-cyclopenta[b]thiophene



Solution of 7g (0.023 mol) 5-methyl-2,3-diphenyl-4,5-dihydro-6H-cyclopenta[*b*]thiophen-6-one in 200ml ether was treated with 0.24g (0.0063mol) LiAlH₄ in 100ml ether. The mixture was stirred in 30 min and then was poured in 300 ml of 10% NH₄Cl. The organic phase was collected, dried over MgSO₄ and evaporated. Resulting alcohol (6.7g, 95%) was dissolved in 350ml benzene. To this solution 0.25g p-toluenesulphonic acid and a few crystals of 2,6-di(tert-butyl)phenol were added. The resulting mixture was refluxed in 10 min, then was cooled to r.t., washed with saturated aq. NaHCO₃ and water. The solution so-obtained was dried over MgSO₄ and evaporated. The residue was recrystallized from hexane to give 4.2g (67% from ketone) of the product as yellowish crystalline solid.

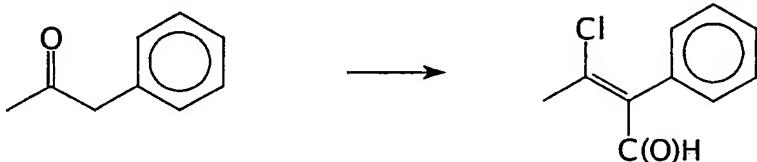
¹H NMR (C₆D₆): 7.45 (d, 2H), 7.31 (d, 2H), 7.15-6.90 (m, 6H), 6.20 (quintet, 1H); 2.73 (br.s, 2H); 1.80 (s, 3H)

Example 2 Synthesis of 2-methyl-3,5-diphenyl-6H-cyclopenta[*b*]thiophene



Preparation of the compound of formula (II)

Synthesis of 3-chloro-2-phenyl-2-butenal



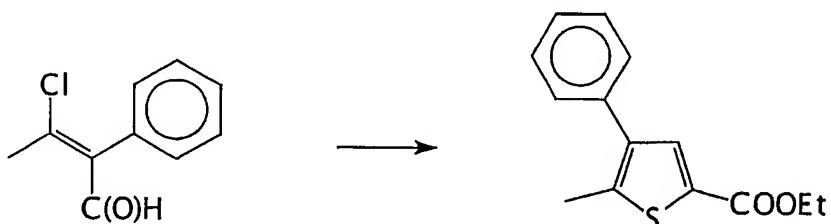
0.375 mol (35 mL) of POCl₃ was added at 0°C to a 0.45 mol (35 mL) of DMF. At the end of the addition, the mixture was allowed to warm up to room temperature and stirred for 30 min. Then it was cooled again to 0°C and carefully treated with 0.15 mol (20.1 g) of phenylacetone. The resulting reaction mixture was stirred at the same temperature for 1 h and then at 60-70°C in additional 4 hours (the reaction was monitored by NMR). The resulting viscous solution was poured into a mixture of ice and aqueous sodium acetate (150g). Product was extracted with CH₂Cl₂ (3 x 50 mL). The organic phase was separated, washed with water until neutral pH, dried over MgSO₄ and evaporated to dryness. The residue represents chloroaldehyde as a mixture of two forms (ratio of forms depends on the duration of

chlorocarbonylation). It was used without further purification. Yield 19.2 (71%).

¹H-NMR (CDCl₃): 10.47(s) and 10.15(s) (1H, CHO); 7.40-7.00 (group of multiplets, 5H, aromatic CH); 2.79(s) and 2.32(s) (3H, CH₃).

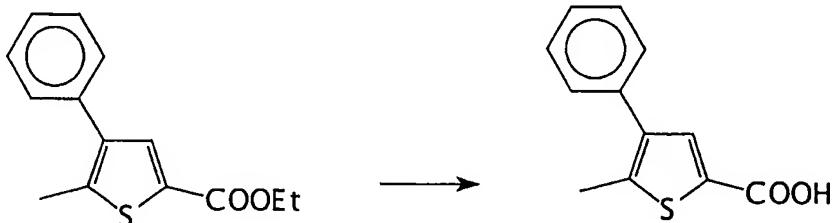
Note: do not use distillation to purify the product!

Synthesis of 5-methyl-4-phenyl-2-thiophene-ethylcarboxylate



Ethyl-2-mercaptopropanoate (45.8 mmol, 5.0 mL) was added at 0°C to a solution of sodium ethoxide (46 mmol, 3.13 g) in 50 mL of ethanol and the resulting mixture was stirred at the same temperature for 30 min. Then 3-chloro-2-phenyl-2-butenal (45.8 mmol, 8.3 g) was added and stirring was continued overnight. The resulting product was refluxed for 2 h, cooled to room temperature and diluted in 100 mL of water. The organic layer was collected and the water layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the residue was used in the next step without further purification.

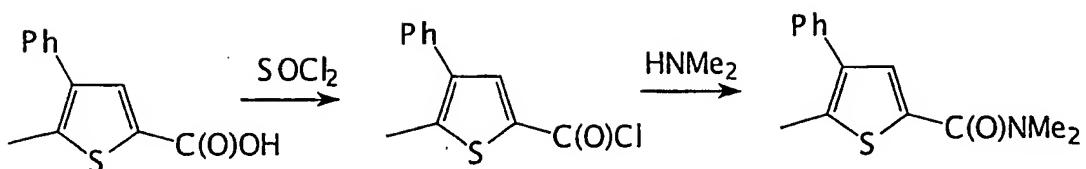
Synthesis of 5-methyl-4-phenyl-2-thiophenecarboxylic acid



The 5-methyl-4-phenyl-2-thiophene-ethylcarboxylate coming from the previous step was added to a 30% solution of sodium hydroxide in 100 mL of ethanol and the resulting mixture was refluxed for 2 h. Then it was diluted in water and extracted with 50 mL of benzene. The water phase was isolated, acidified and the mixture was filtered. The precipitate was dried under P₂O₅. Yield 9.5 g (95% towards 3-chloro-2-phenyl-2-butenal).

¹H-NMR (CDCl₃): 12.00-10.00 (br.s, 1H, COOH); 7.87 (s, 1H, thiopheneCH); 7.50-7.35 (m, 5H, phenylCH); 2.58 (s, 3H, CH₃).

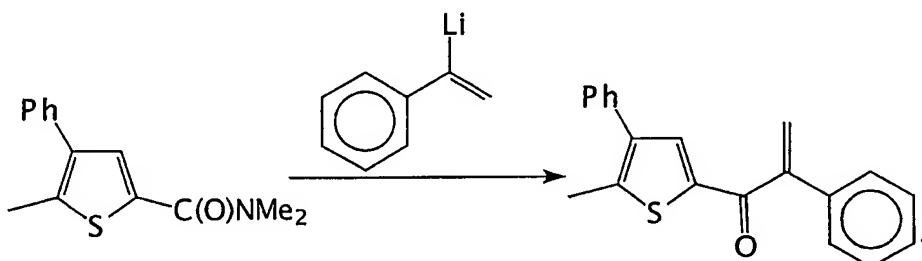
Synthesis of 2-Methyl-3-phenyl-thienylcarbonyc dimethylamide



21.8g (0.1mol) of acid, 10.9ml SOCl_2 (0.15mmol), 0.5ml DMF and 150 ml of dichloromethane were placed into the bulb and refluxed in 2h. Then the mixture was evaporated. Resulting oil was dissolved in 20ml THF and this solution was added dropwise to 50ml 33% aqueous Me_2NH at 0°C. The mixture was stirred in 30min. The resulting emulsion was poured into 500ml of water. Product was extracted with 2x50ml dichloromethane. Solution was washed with water, dried over magnesium sulfate and evaporated to give brown viscous liquid that tends to crystallize. Yield 28g (81%).

^1H NMR (CDCl_3): 7.45 (s, 1H), 7.40-7.20 (m, 10H), 3.40-3.20 (br.s., 6H)

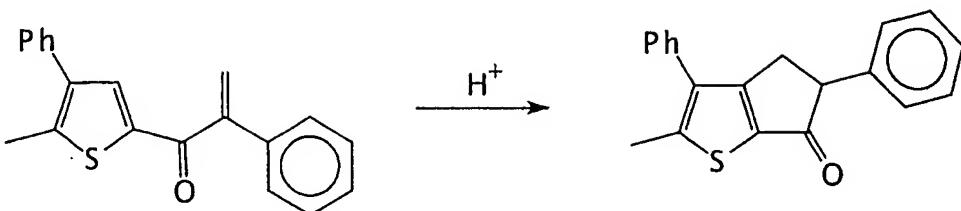
Step a) 1-(5-Methyl-4-phenyl-2-thienyl)-2-phenyl-2-propen-1-on



23.3g (100mmol) of 2-methyl-3-phenyl-thienylcarboxylic acid dimethylamide was mixed with 100ml ether and the resulting suspension was added in some portions at 0°C to solution of 1-stiryllithium prepared from 62ml 1.6M BuLi in hexane (100mmol) and 27g 1-bromostyrene (150mmol) in 200ml ether. The mixture warmed to r.t. and was stirred in 1h. The resulting solution was poured into 500ml of 5% aqueous HCl. The organic phase was collected, separated from insoluble impurities (these impurities presumably are due to the use of Li-derivative instead of Mg derivative in the previous case), washed with water, dried over MgSO_4 and evaporated to give yellow oil. Yield of crude product 15g (52%). The product can be contaminated with 5-10% of starting amide (by NMR) and can be used without further purification.

^1H NMR (CDCl_3): 7.61 (s, 1H), 7.55-7.35 (m, 10H), 6.03 (s, 1H), 5.82 (s, 1H), 2.59 (s, 3H)

Step b) 2-Methyl-3,5-diphenyl-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on

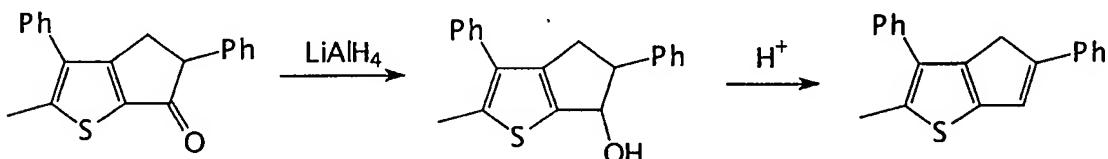


Vinyl-ketone obtained in previous experiment was dissolved in 20ml of dichloromethane and resulting was poured into 50 ml methanesulphonic acid heated to 65°C. After 30 min of stirring at reflux the resulting mixture was poured into the mixture 0.31 water/ice/200ml dichloromethane. The organic phase was collected, washed with water, then with aq. NaHCO₃ up to neutral reaction and dried over MgSO₄. The resulting solution was evaporated to give 14g of viscous oil. This oil crystallizes on standing. This substance can be used for further steps (reduction by LiAlH₄ followed by dehydration without special purification).

¹H NMR (CDCl₃): 7.55-7.20 (m, 10H), 4.15 (dd, 1H); 3.50 (dd, 1H); 3.07 (dd, 1H), 2.61 (s, 3H)

Steps c) and d)

2-Methyl-3,5-diphenyl-4H-cyclopenta[b]thiophene

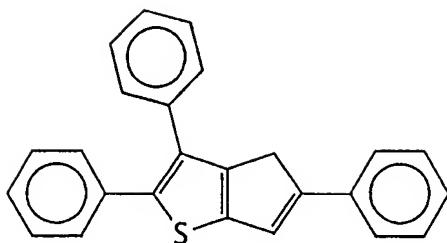


Solution of 14g (47mmol) 2-Methyl-3,5-diphenyl-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on in 150ml ether was treated with 0.63g (16mmol) LiAlH₄ in 100ml ether. The mixture was stirred in 30 min and then was poured in 300 ml of 10% NH₄Cl. The organic phase was collected, dried over MgSO₄ and evaporated. Resulting alcohol (13.4g, 95%) was poured into solution 1g p-toluenesulphonic acid in 1l toluene at 65°C. The resulting mixture was stirred in 20 min at 80°C, then it was cooled to r.t., washed with saturated aq. NaHCO₃ and water. The solution so-obtained was dried over MgSO₄ and evaporated. The residue was isolated by chromatography on silica-gel (hexane/CH₂Cl₂ 3/1) to give 6.5g (53% from ketone) of yellowish crystalline solid. This solid consists of two isomers of position of double bond.

¹H NMR (CDCl₃): 7.60-7.20 (m, 10H), 7.21(m) and 7.14(m) (1H), 3.83 (br.s) and 3.68 (br.s) 2H); 2.60 (s, 3H)

Example 3

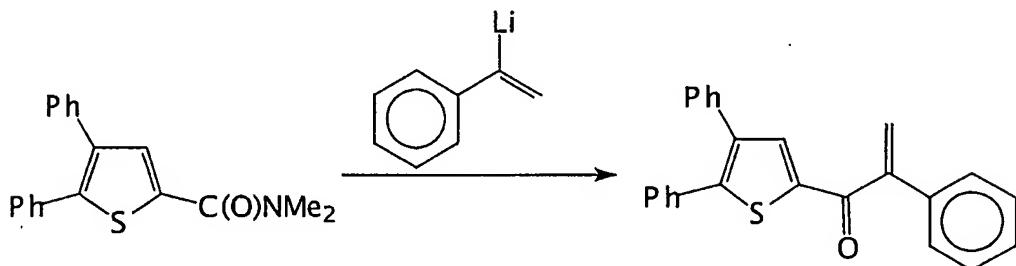
Synthesis of 2,3,5-triphenyl-6H-cyclopenta[b]thiophene



Preparation of the compound of formula (II)

2,3-diphenyl-thienylcarbonyc acid dimethylamide was prepared in analogous manner to 2-Methyl-3-phenyl-thienylcarbonyc dimethylamide with the exception that the starting compound was dibenzyl ketone instead of phenylacetone.

Step a) 1-(4,5-Diphenyl-2-thienyl)-2-phenyl-2-propen-1-on

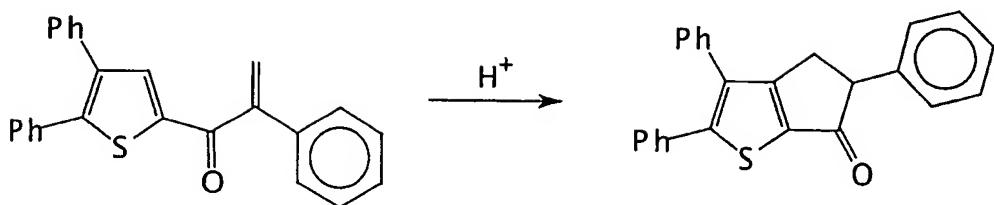


30.7g (100mmol) of 2,3-diphenyl-thienylcarbonyc acid dimethylamide was mixed with 100ml ether and the resulting suspension was added in some portions at 0°C to solution of 1-styryllithium prepared from 62ml 1.6M BuLi in hexane (100mmol) and 27g 1-bromostyrene (150mmol) in 200ml ether. The mixture warmed to room temperature (r.t.) and was stirred for 1h. The resulting solution was poured into 500ml of 5% aqueous HCl. The organic phase was collected, separated from insoluble impurities, washed with water, dried over MgSO₄ and evaporated to give 20.9g (57%) of crystalline solid. The product can be contaminated with 5-10% of starting amide (by NMR) and can be used without further purification.

¹H NMR (CDCl₃): 7.82 (s, 1H), 7.70-7.30 (m, 15H), 6.16 (s, 1H), 5.96(s, 1H)

Note: technical-grade 1-bromo-styrene is available only. It was distilled before reaction and was taken in 50% excess.

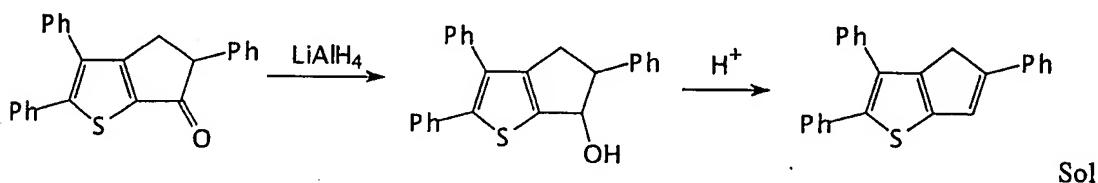
Step b) 2,3,5-triphenyl-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on



Vinyl-ketone obtained in previous experiment was dissolved in 20ml of dichloromethane and resulting was poured into 50 ml methanesulphonic acid heated to 65°C. After 30 min of stirring at reflux the resulting mixture was poured into the mixture 0.31 water/ice/200ml dichloromethane. The organic phase was collected, washed with water, then with aq. NaHCO₃ up to neutral reaction and dried over MgSO₄. The resulting solution was evaporated to give 20g of crystalline product. This substance can be used for further steps (reduction by LiAlH₄ followed by dehydration) without special purification.

¹H NMR (CDCl₃): 7.55-7.20 (m, 15H), 4.25 (dd, 1H); 3.61 (dd, 1H); 3.20 (dd, 1H)

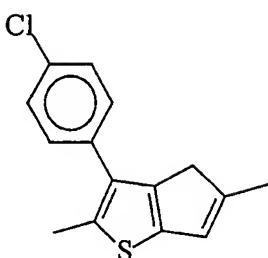
Steps c) and d) 2,3,5-Triphenyl-4H-cyclopenta[b]thiophene



Solution of 3.7g (10mmol) 2,3,5-triphenyl-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on in 20ml ether was treated with 130mg (16mmol) LiAlH₄ in 10ml ether. The mixture was stirred in 30 min and then was poured in 50 ml of 10% NH₄Cl. The organic phase was collected, dried over MgSO₄ and evaporated. Resulting alcohol was poured into solution of 300mg p-toluenesulphonic acid in 300ml toluene at 65°C. The resulting mixture was refluxed in 20 min, then it was cooled to r.t., washed with saturated aq. NaHCO₃ and water. The solution so obtained was dried over MgSO₄ and evaporated. The residue was isolated by chromatography on silica-gel (hexane/CH₂Cl₂ 3/1) to give 2.1g (60% from ketone) of yellowish crystalline solid.

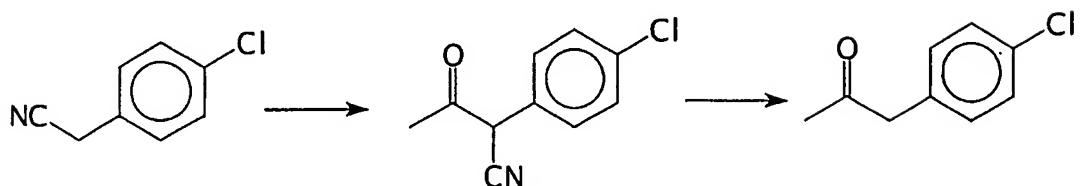
¹H NMR (CDCl₃): 7.60 (m, 2H), 7.45-7.25(m, 14H); 3.72 (d, 2H)

Example 3 Synthesis of 2,5-dimethyl-3-(4-chloro-phenyl)-6H-cyclopenta[b]thiophene



Preparation of the compound of formula (II)

Synthesis of (4-chloro-phenyl)-acetone



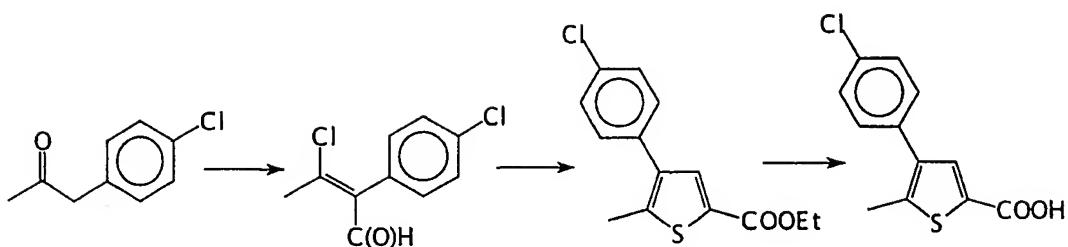
34g (0.224mol) (4-chloro-phenyl)benznitril and 33ml (0.337mol) ethylacetate was added to the hot solution of 24g (0.3mol) sodium isopropilate in 150ml isopropanol. Reaction mixture was stirred at reflux in 3 hours then it was cooled to r.t., treated with 20g (0.3mol) acetic acid and finally diluted with 500ml water. Organic precipitate was extracted with 100ml dichloromethane. Resulting solution was evaporated to give yellowish solid of p-Cl-phenylacetone that was used without purification.

¹H-NMR (CDCl₃): 7.44 (AA'BB' component, 2H); 7.36 (AA'BB' component, 2H); 4.68 (s, 1H); 2.31 (s, 3H).

p-Cl-phenylacetone prepared in previous experiment was added in small portions to 50ml of concentrated sulfuric acid at 0-5°C then the mixture was heated at stirring to 100°C in 10min. Then the reaction mixture was cooled to 0°C, was treated quickly with 250ml water and was stirred at 100°C in 3 hours. The resulting mixture was cooled to r.t., the organic layer was separated and distilled at 108-110/10torr to give 24.5g (65% from p-Cl-phenylacetone).

¹H-NMR (CDCl₃): 7.34 (AA'BB' component, 2H); 7.16 (AA'BB' component, 2H); 3.71 (s, 2H); 2.20 (s, 3H).

Synthesis of 5-methyl-4-(4-Cl-phenyl)-2-thiophenecarboxylic acid

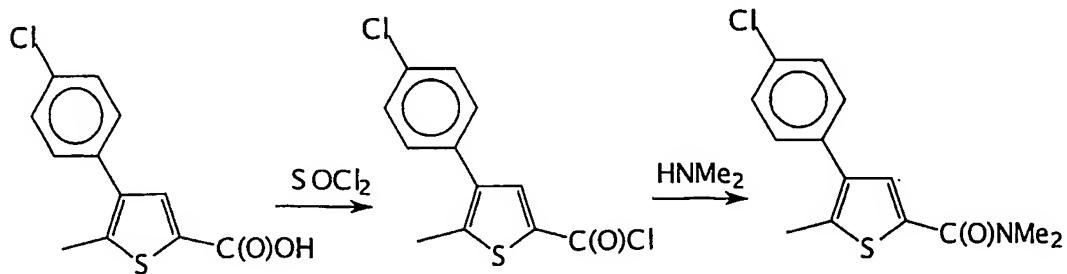


17.5ml (0.19 mol) of POCl_3 was added at 0°C to a 32ml (0.44mol) of DMF. At the end of the addition, the mixture was allowed to warm up to room temperature and stirred for 30 min. Then it was cooled again to 0°C and carefully treated with 24.5g (0.145 mol) of p-Cl-phenylacetone. The resulting reaction mixture was stirred at the same temperature for 1 h and then at $60\text{-}70^\circ\text{C}$ in additional 4 hours. The resulting viscous solution was poured into a mixture of ice and aqueous sodium acetate (150g). Product was extracted with CH_2Cl_2 (3×50 mL). The organic phase was separated, washed with water until neutral pH, dried over MgSO_4 and evaporated to dryness. The residue represents 21.5 g (68%) of crude chloroaldehyde that was used as is.

Ethyl-2-mercaptoacetate (12g, 0.1mol) was added at 0°C to a solution of sodium ethoxide (6.8g, 0.1mol) in 150 mL of ethanol and the resulting mixture was stirred at the same temperature for 30 min. Then chloroaldehyde from the previous experiment (21.5g, 0.1mol) was added and stirring was continued overnight. The resulting product was refluxed for 2 h, cooled to room temperature and then was treated with solution of 12g (0.3mol) NaOH in 20ml water. The resulting mixture was refluxed in 1 hour, then it was cooled to r.t. and finally was poured into 500ml of water. The resulting mixture was neutralized by aqueous HCl, the precipitate was isolated, washed twice with 200ml water and dried. Yield 15.3g (60%).

$^1\text{H-NMR}$ (DMSO): 7.52 (s, 1H, thiopheneCH); 7.47 (m, 4H, phenylCH); 2.46 (s, 3H, CH_3).

Synthesis of 2-Methyl-3-(4-chlorophenyl)-thienylcarbonyl dimethylamide

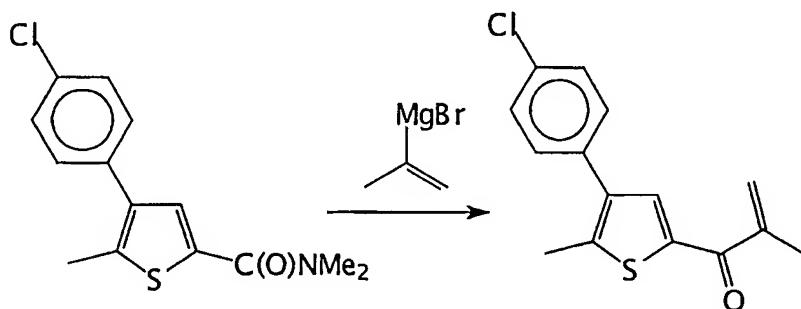


15.3g (0.06mol) of acid, 7.1ml SOCl_2 (0.1mmol), 0.1ml DMF and 100 ml of dichloromethane were placed into the bulb and refluxed in 30min. Then the mixture was evaporated. Resulting

oil was dissolved in 20ml THF and this solution was added dropwise to 50ml 33% aqueous Me₂NH at 0°C. The mixture was stirred in 30min. The resulting emulsion was poured into 500ml of water. Product was extracted with 2x50ml dichloromethane. Solution was washed with water, dried over magnesium sulfate and evaporated to give brown viscous liquid. Yield 14.4g (86%).

¹H-NMR (CDCl₃): 7.45-7.30 (m, 5H); 3.25 (br.s, 6H); 2.50 (s, 3H).

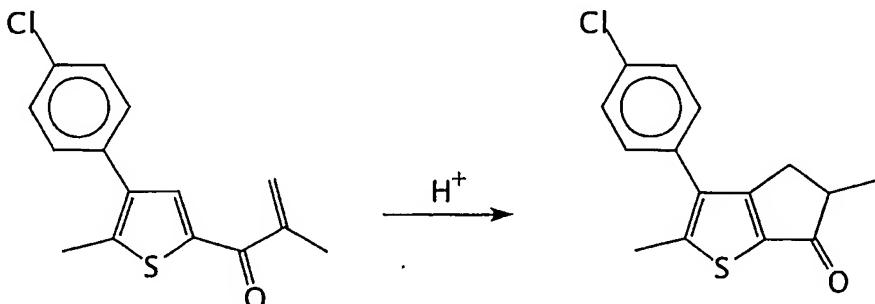
Step a) 1-[5-Methyl-4-(4-chloro-phenyl)-2-thienyl]-2-methyl-2-propen-1-on



7.2g (26mmol) of 2-methyl-3-(p-Cl-phenyl)-thienylcarboxylic acid dimethylamide was dissolved in 15ml THF and the resulting solution was added dropwise to solution of 2-propenylmagnesium bromide prepared from 1g Mg (42mmol) and 3.7g 2-bromopropene (31mmol) in 20ml THF at 0°C. The mixture warmed to r.t. and was stirred in 4h. The resulting solution was poured into 100ml of 5% aqueous HCl. The organic layer was collected, washed with water, dried over MgSO₄ and evaporated to give quantitative amount yellow-reddish oil that was used without further purification.

¹H NMR (CDCl₃): 7.56 (s, 1H); 7.39 (AA'BB' component, 2H); 7.29 (AA'BB' component, 2H); 5.79 (m, 1H), 5.74 (m, 1H), 2.51 (s, 3H); 2.04 (m, 3H)

Step b) 2,5-Dimethyl-3-(4-chloro-phenyl)-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on

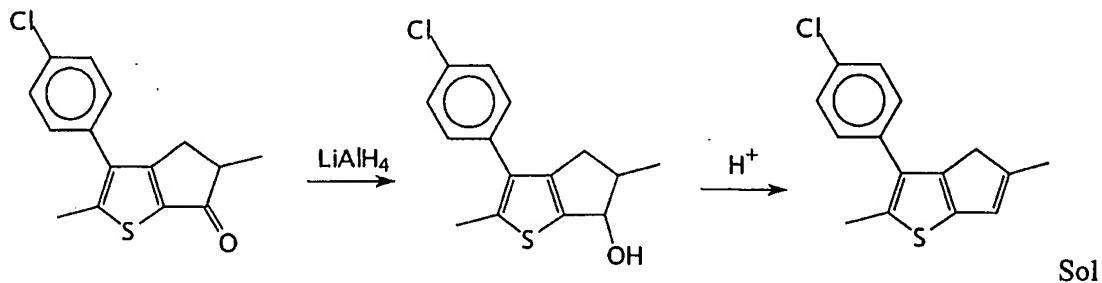


Vinyl-ketone obtained in previous experiment was dissolved in 10ml of dichloromethane and

resulting solution was poured into 25 ml methanesulphonic acid heated to 65°C. After 20 min of stirring at reflux the resulting mixture was poured into the mixture 0.2l water/ice/50ml dichloromethane. The organic phase was collected, washed with water, then with aq. NaHCO₃ up to neutral reaction and dried over MgSO₄. The resulting solution was evaporated and was purified by chromatography (hexane/ether 3/1) to give 2.2g (31%) of viscous oil.

¹H NMR (CDCl₃): 7.41 (AA'BB' component, 2H); 7.23 (AA'BB' component, 2H); 3.13 (dd, 1H), 2.94 (quintet of doublets, 1H); 2.50 (s, 3H); 2.49 (dd, 1H), 1.31 (d, 3H)

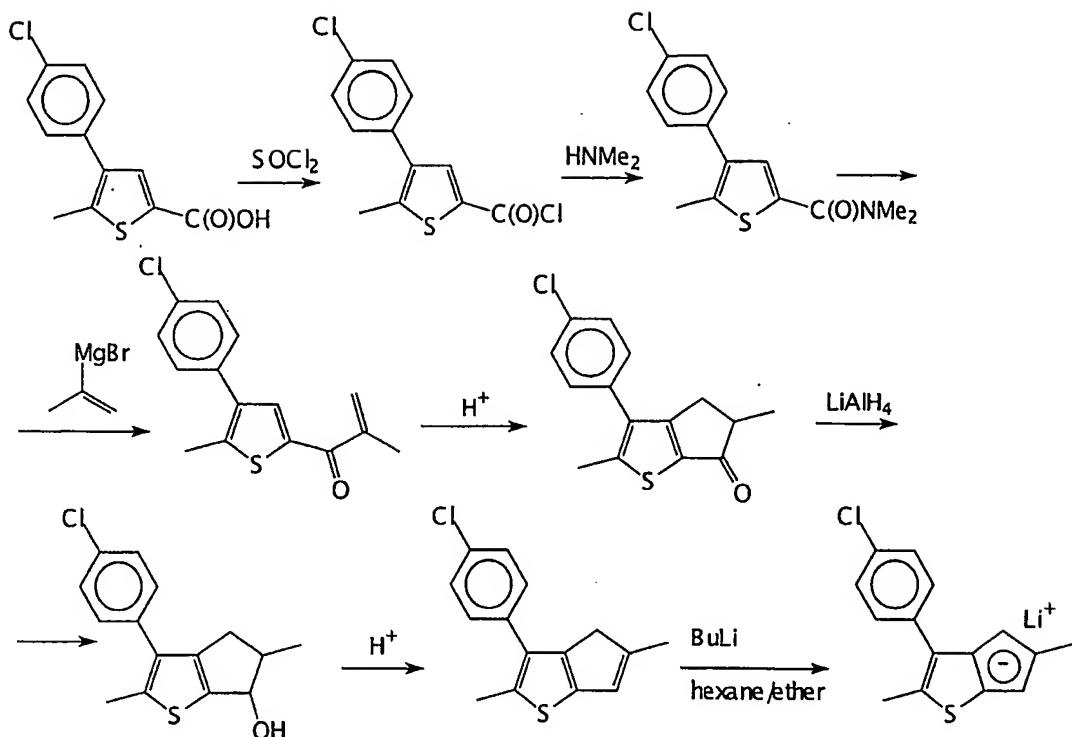
Steps c) and d) Synthesis of 2,5-dimethyl-3-(4-chloro-phenyl)-6H-cyclopenta[b]thiophene



ution of 2.2g (8mmol) 2,5-dimethyl-3-(4-chloro-phenyl)-4,5-dihydro-6H-cyclopenta[b]thiophen-6-on in 20ml ether was treated with 0.1g (2.6mmol) LiAlH₄ in 20ml ether. The mixture was stirred in 30 min and then was poured in 30 ml of 10% NH₄Cl. The organic phase was collected, dried over MgSO₄ and evaporated. Resulting alcohol was dissolved in 150ml benzene. To this solution 0.1g p-toluenesulphonic acid. The resulting mixture was refluxed in 10 min, then was cooled to r.t., washed with saturated aq. NaHCO₃ and water. The solution so-obtained was dried over MgSO₄ and evaporated to give 1.4g (67% from ketone) of the solid product.

¹H NMR (CD₂Cl₂): 7.37 (AA'BB' component, 2H); 7.32 (AA'BB' component, 2H); 6.38 (quintet, 1H); 3.06 (br.s., 2H); 2.43 (s, 3H); 2.10 (br.s, 3H).

Example 4 one pot Synthesis of 2,5-dimethyl-3-(4-chloro-phenyl)-6H-cyclopenta[b]thiophene lithium salt



15.3g (0.06mol) of acid, 7.1ml SOCl_2 (0.1mmol), 0.1ml DMF and 100 ml of dichloromethane were placed into the bulb and refluxed in 30min. Then the mixture was evaporated. Resulting oil was dissolved in 20ml THF and this solution was added dropwise to 50ml 33% aqueous Me_2NH at 0°C. The mixture was stirred in 30min. The resulting emulsion was poured into 500ml of water. Product was extracted with 2x50ml dichloromethane. Solution was washed with water, dried over magnesium sulfate and evaporated to give brown viscous liquid.

Viscous liquid so-obtained was dissolved in 15ml THF and the resulting solution was added dropwise to solution of 2-propenylmagnesium bromide prepared from 2g Mg (42mmol) and 7.4g 2-bromopropene (62mmol) in 40ml THF at 0°C. The mixture warmed to r.t. and was stirred in 4h. The resulting solution was poured into 200ml of 5% aqueous HCl. The organic layer was collected, washed with water, dried over MgSO_4 and evaporated to give yellow-reddish oil of vinyl-ketone.

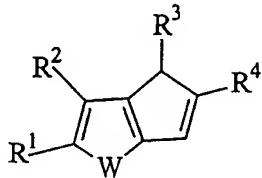
Vinyl-ketone obtained in previous experiment was dissolved in 20ml of dichloromethane and resulting solution was poured into 50 ml methanesulphonic acid heated to 65°C. After 20 min of stirring at reflux the resulting mixture was poured into the mixture 0.4l water/ice/100ml dichloromethane. The organic phase was collected, washed with water, then with aq. NaHCO_3

up to neutral reaction and dried over $MgSO_4$. The resulting solution was evaporated, then was dissolved in 50ml ether was treated with 675mg (15mmol) $LiAlH_4$ in 50ml ether. The mixture was stirred in 30 min and then was poured in 30 ml of 10% NH_4Cl . The organic phase was collected, dried over $MgSO_4$ and evaporated. Resulting alcohol was dissolved in 300ml toluene. To this solution 0.2g p-toluenesulphonic acid was added. The resulting mixture was heated under stirring at 80°C in 10 min, then was cooled to r.t., washed with saturated aq. $NaHCO_3$ and water. The solution so-obtained was dried over $MgSO_4$ and evaporated to give 10.4g of crude ligand.

This crude product was dissolved in the mixture of 30ml ether and 100ml hexane and then was treated with 38ml of 1.6M $BuLi$ in hexane (60mmol). The precipitate was isolated, washed with hexane and dried. Yield 7.5g.

CLAIMS

1. A process for preparing heterocyclic pentalene derivatives having formula (I):



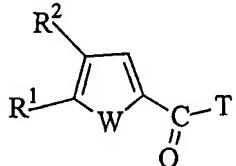
(I)

wherein

W is a sulfur atom, an oxygen atom or a NR or PR group wherein R is selected from the group consisting of a linear or branched saturated or unsaturated C₁-C₂₀-alkyl, C₃-C₂₀-cycloalkyl, C₆-C₂₀-aryl, C₇-C₂₀-alkylaryl and C₇-C₂₀-arylalkyl radical, optionally containing heteroatoms belonging to groups 13-17 of the Periodic Table of the Elements; R¹, R², R³ and R⁴, equal to or different from each other, are hydrogen atoms or a linear or branched saturated or unsaturated C₁-C₂₀-alkyl, C₃-C₂₀-cycloalkyl, C₆-C₂₀-aryl, C₇-C₂₀-alkylaryl or C₇-C₂₀-arylalkyl radical, optionally containing heteroatoms belonging to groups 13-17 of the Periodic Table of the Elements; or R¹ and R² and/or R³ and R⁴ can form a C₄-C₇ ring optionally containing O, S, N, P or Si atoms, said ring optionally bearing C₁-C₂₀ alkyl substituents or being optionally fused with a C₄-C₇ ring optionally containing O, S, N, P or Si atoms;

said process comprising the following steps:

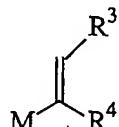
a) contacting a compound of formula (II):



(II)

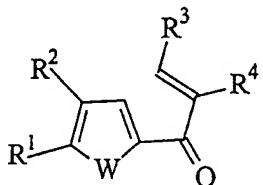
wherein R¹ and R² are defined as above and T is a OR, NR₂, OH, CCl₃, CF₃, Cl, Br, I, imidazolyl or pirazolyl radical;

with at least one molar equivalent of a vinyl compound of formula (III):



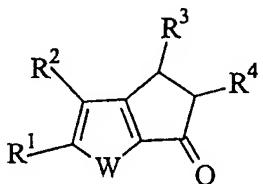
(III)

wherein R^3 and R^4 are defined as above and M is MgHal, Li, K, ZnHal, wherein Hal is chlorine, bromine or iodine; to form a compound of formula (IV)



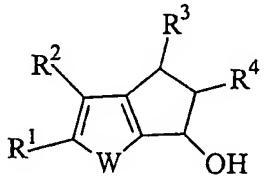
(IV)

b) treating the compound of formula (IV) with a Brønsted acid to form a compound of formula (V):



(V)

c) treating the compound of formula (V) with a reducing agent to form the correspondent alcohol of formula (VI);



(VI)

and

d) dehydrating the alcohol of formula (VI).

2. The process according to claim 1 wherein in the compound of formula (I) the group NR is N-methyl or N-phenyl; the group PR is P-methyl or P-phenyl; R^1 is hydrogen, a C_1 - C_{20} -alkyl or C_7 - C_{20} -arylalkyl radical; R^2 is hydrogen or a C_7 - C_{20} -arylalkyl radical; R^3 is hydrogen or a C_1 - C_{20} -alkyl radical and R^4 is hydrogen, a C_1 - C_{20} -alkyl or C_7 - C_{20} -arylalkyl radical.

3. The process according to claims 1 or 2 wherein in the compound of formula (I) W is a sulfur atom; R^1 is a methyl, a phenyl or a C_1 - C_{10} alkyl substituted phenyl radical; R^2 is a

phenyl or a C₁-C₁₀ alkyl-substituted phenyl radical and R⁴ is a methyl, or a phenyl radical.

4. The process according to anyone of claims 1 to 3 wherein in the compound of formula (II) T is NR₂ group and in the compound of formula (III) the group M is MgBr or Li.
5. The process according to anyone of claims 1 to 4 wherein the Brønsted acid used in step b) are methanesulphonic acid, sulfuric acid, phosphoric acid, polyphosphoric acid or P₂O₅/methansulfuric acid.
6. The process according to anyone of claims 1 to 5 wherein the reducing agent used in step c) is LiAlH₄, AlH₃, NaBH₄ or LiHAl(OtBu)₃.
7. The process according to anyone of claims 1 to 6 wherein the dehydrating agent used in step d) is p-toluenesulfonic acid, sulfuric acid, hydrochloric acid or iodine.
8. The process according to anyone of claims 1 to 7 wherein the compound obtained in step d) is purified by treating the crude reaction product with at least one equivalent of an organolithium compound and filtering the obtained salt.
9. The process according to anyone of claims 1 to 8 wherein steps a), b), c) and d) are carried out in sequence without purification of the intermediate products.
10. The process according to anyone of claims 1 to 8 wherein steps c) and d) are carried out without purification of the alcohol of formula (VI).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07680A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D33/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MINORU ISHIKURA ET AL: "A Concise Preparation of Yuehchukene And Its Analogues" HETEROCYCLES, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 53, no. 10, 2000, pages 2201-2220, XP001093781 ISSN: 0385-5414 *Schemes 1 and 3* example 9; tables 1,2 ---	1-10
A	WO 01 44318 A (BASELL TECHNOLOGY COMPANY B V ;EWEN JOHN A (US); ELDER MICHAEL J () 21 June 2001 (2001-06-21) cited in the application examples 1-3 --- ---	1-10 ---

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2002	17/10/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Härtinger, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07680

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; METH-COHN, OTTO ET AL: "Thiophene analogs of indenes. II. Synthesis, tautomerism, and metalation of the thiophene analogs of 2-methylindene" retrieved from STN Database accession no. 67:21765 XP002215127 abstract & ACTA CHEM. SCAND. (1966), 20(7), 1733-42 ,</p> <p>---</p>	1-10
A	<p>US 5 252 749 A (BADORC ALAIN ET AL) 12 October 1993 (1993-10-12) column 7, last paragraph -column 8, line 50; table 1</p> <p>---</p>	1-10
Y	<p>DATABASE CROSSFIRE BEILSTEIN 'Online! BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Reaction ID 264677, XP002215128 abstract & MAXIM ET AL: BULLETIN DE LA SOCIETE CHIMIQUE FRANCAIS, vol. 5, no. 6, 1939, pages 1339-1345, -----</p>	1-10

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 02/07680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1, 2 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 02 07680

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2

Present claim 1 relates to an extremely large number of possible products obtainable by the claimed process. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products, namely those pentalene derivatives of the formula I, wherein R1/R2 or R3/R4 is either not fused or represents a monocyclic or bicyclic carbocycle; and any of the optional heteroatoms is selected from sulfur, nitrogen, oxygen or halogen. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible, also due to the fact that no teaching is given as to how to obtain compounds comprising heteroatoms other than the above mentioned. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the individualised thiophen examples and there oxa and aza analogues, i.e. W = S, N, O.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/EP 02/07680

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0144318	A 21-06-2001	US 6444833 B1		03-09-2002
		AU 3007901 A		25-06-2001
		BR 0010043 A		22-01-2002
		CN 1347424 T		01-05-2002
		WO 0144318 A1		21-06-2001
		EP 1153047 A1		14-11-2001
		PL 349318 A1		15-07-2002
US 5252749	A 12-10-1993	AT 157360 T		15-09-1997
		AU 652072 B2		11-08-1994
		AU 2454892 A		01-04-1993
		BR 9203744 A		29-03-1994
		CA 2079016 A1		26-03-1993
		CZ 9202918 A3		14-04-1993
		DE 69221802 D1		02-10-1997
		DE 69221802 T2		02-04-1998
		DK 534856 T3		20-04-1998
		EP 0534856 A1		31-03-1993
		ES 2108098 T3		16-12-1997
		FI 924281 A		26-03-1993
		GR 3025335 T3		27-02-1998
		HU 62876 A2		28-06-1993
		IL 103106 A		15-06-1998
		JP 3162822 B2		08-05-2001
		JP 5213932 A		24-08-1993
		KR 199848 B1		15-06-1999
		MX 9205390 A1		01-05-1993
		NO 923720 A		26-03-1993
		NZ 244452 A		26-08-1994
		PH 30225 A		05-02-1997
		RU 2060253 C1		20-05-1996
		ZA 9207318 A		24-03-1994